by Leiser and Biel.[11] To 100.2 g. (1.0 mole) of *N*-methyl piperazine dissolved in 1 l. of anhydrous methanol was added dropwise and with stirring a solution of 44 g. (1.0 mole) of ethylene oxide in 100 ml. of dry toluene. The mixture was stirred for an additional 3 hr. and was permitted to stand overnight. The solvents were removed by distillation, and the residue was fractionated, the liquid boiling at 90–92 (3.0 mm.) being collected. The yield was 91 g. (63%).

Methyl esters. All of the methyl esters except methyl α,α-diphenylmethoxyacetate were prepared by treating an ethereal solution or suspension of the acid with an eightfold excess of an ethereal solution of diazomethane. After effervescence had ceased, the ether and excess diazomethane were removed on a steam bath, and the crude methyl ester was purified by recrystallization or distillation to give an almost quantitative yield. See Table I.

Transesterifications. The methyl ester of the carboxylic acid (0.02 mole) was placed together with an equimolecular portion of the amino alcohol in a 1-l. three necked flask seated in a mantle, and equipped with a Hershberg stirrer and a Dean-Stark moisture determination apparatus topped with a condenser and a calcium chloride tube. Dry *n*-heptane (600 ml.) and 100 mg. of solid sodium methoxide were added to the flask, and the contents were heated and stirred. After an hour's refluxing, an additional 100 mg. of sodium methoxide was added. From time to time, the contents of the Dean-Stark apparatus were drained and discarded, and fresh portions of *n*-heptane were added to the flask so as to maintain the original volume. After 8 hr. refluxing, an additional 50 mg. portion of sodium methoxide was added. Refluxing was continued for a total of 15 hr.; the reaction mixture was then cooled and transferred to a separatory funnel. The organic mixture was extracted repeatedly with water until the washings were approximately *p*H 7. The solvent was removed from the organic solution under reduced pressure from a steam bath; the residue of crude heterocyclic ester was dissolved in ether and this solution was dried over anhydrous magnesium sulfate and filtered. The salt of the ester was prepared from this solution.

Hydrochlorides of the heterocyclic esters. A saturated solution of anhydrous hydrogen chloride in anhydrous ether was added to the dried ethereal solution of the crude amino ester until no more precipitation occurred. The crude hydrochloride was collected on a suction filter, washed with anhydrous ether, and recrystallized.

Bifumarates of the heterocyclic esters. An excess of recrystallized, dried fumaric acid was stirred with 1.5 l. of anhydrous ether for 1 hr., so as to prepare a saturated solution. This solution was filtered through a gravity filter directly into a 3-l. Erlenmeyer flask containing 0.01–0.05 mole of crude amino ester dissolved in 500 ml. of dried ether. The resulting clear solution was placed in a refrigerator for several days, during which time the bifumarate salt slowly crystallized from solution. It was collected on a suction filter and recrystallized.

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(11) H. A. Leiser and J. H. Biel, Lakeside Laboratories, Milwaukee. Personal communication. J. Cymerman-Craig R. J. Harrisson, M. E. Tate, R. H. Thorp, and R. Ladd [*Australian J. Chem.*, 9, 89 (1956)] prepared this compound from 1-(2-hydroxyethyl)piperazine by a Leuckart Reaction. b.p. 88° (3 mm.).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTH TEXAS STATE COLLEGE]

Amebicides. I. Some 1-(1,4-Dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)-pyridinium Betaines

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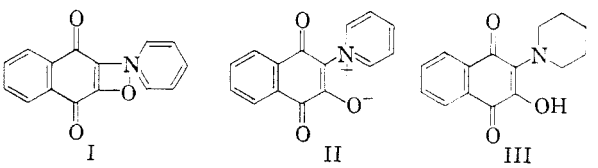
The reaction of 2,3-dichloro-1,4-naphthoquinone with pyridine has been extended to various 2-, 3-, and 4-substituted pyridines and corresponding 1-(1,4-dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)-substituted pyridinium betaines were obtained when acetic acid was used as the solvent for the reaction. The reduction of some of these betaines to 2-hydroxy-3-piperidino-1,4-naphthoquinones is described. The amebicidal activities of these compounds are summarized.

A study and use of the reaction between 2,3-dichloro-1,4-naphthoquinone and pyridine as reported by Ullman and Ettisch,[3] was undertaken in order to obtain a number of pyridinium compounds of a heretofor unstudied group for evaluation as antitubercular and amebicidal agents.[4] Ullmann and Ettisch reported the isolation of 3-hydroxy-1,4-naphthoquinone-2-pyridinium anhydride (I) from the reaction of pyridine and 2,3-dichloro-1,4-naphthoquinone in refluxing alcohol. We prefer to use structure II, 1-(1,4-dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)pyridinium betaine, to represent this type of compound.

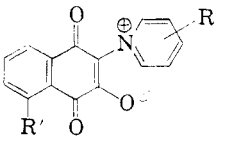


When we attempted to extend the reaction by the use of 4-(1-octyl)pyridine, a dark red oil was obtained, which was converted with much difficulty to a reddish-purple solid. However, when the initial reaction between 4-(1-octyl)pyridine and 2,3-dichloro-1,4-naphthoquinone was performed in

(1) Research Fellows of Research Corporation, 1950–52.
(2) Research Fellows of Parke, Davis & Co., 1950–53.
(3) F. Ullmann and M. Ettisch, *Ber.*, **54B**, 259 (1921).
(4) Price Truitt, Burl Bryant, William E. Goode, and B. Arnwine, *J. Am. Chem. Soc.*, **74**, 2179 (1952).

TABLE I

1-(1,4-DIHYDRO-1,4-DIOXO-3-HYDROXY-2-NAPHTHYL)PYRIDINIUM BETAINES



	R′	R	M.P.°	Yield, %	Formula	Analysis, % Nitrogen Calcd.	Found
1	H	H	302–303	80	$C_{15}H_9O_3N$	5.58	5.64
2	H	2-Methyl	160–161	33	$C_{16}H_{11}O_3N$	5.29	5.40
3	H	3-Methyl	263–265	65	$C_{16}H_{11}O_3N$	5.29	5.37
4	H	4-Methyl	319 dec.	80	$C_{16}H_{11}O_3N$	5.29	5.42
5	H	4-(1-Pentyl)	239–241	70	$C_{20}H_{19}O_3N$	4.36	4.41
6	H	4-(1-Hexyl)	229–230	80	$C_{21}H_{21}O_3N$	4.18	4.20
7	H	4-(1-Octyl)	230–231	70	$C_{23}H_{25}O_3N$	3.86	3.91
8	H	4-(1-Nonyl)	208–210	75	$C_{24}H_{27}O_3N$	3.74	3.80
9	H	4-(1-Tridecyl)	155–157	65	$C_{28}H_{35}O_3N$	3.24	3.20
10	H	2,4-Dimethyl	161–163	40	$C_{17}H_{13}O_3N$	5.00	5.11
11	H	2,6-Dimethyl	172–173	30	$C_{17}H_{13}O_3N$	5.00	4.92
12	H	2-(1-Pentyl)	171–172	55	$C_{20}H_{19}O_3N$	4.36	4.45
13	H	2-(1-Hexyl)	184–185	60	$C_{21}H_{21}O_3N$	4.18	3.89
14	H	4-(Cyclohexylmethyl)	201–207	85	$C_{22}H_{21}O_3N$	4.03	3.56
15	H	4-(3-Cyclohexylpropyl)	218–219	65	$C_{24}H_{25}O_3N$	3.74	3.69
16	H	4-(1-Cyclohexylbutyl)	215–220	65	$C_{25}H_{27}O_3N$	3.59	3.66
17	H	4-(1-Cyclohexylpentyl)	178–183	78	$C_{26}H_{29}O_3N$	3.47	3.64
18	H	4-(3-Methylcyclohexylmethyl)	169–172	63	$C_{24}H_{25}O_3N$	3.88	3.97
19	H	4-(4-Ethylcyclohexylmethyl)	193–195	61	$C_{24}H_{25}O_3N$	3.74	3.87
20	H	4-(4-Methylcyclohexylmethyl)	199–200	60	$C_{23}H_{23}O_3N$	3.88	3.95
21	H	4-(2-Methylcyclohexylmethyl)	184–187	55	$C_{23}H_{23}O_3N$	3.88	3.91
22	H	4-(3,4-Dimethylcyclohexylmethyl)	167 dec.	35	$C_{24}H_{25}O_3N$	3.74	3.93
23	H	4-(3,5-Dimethylcyclohexylmethyl)	152–153	45	$C_{24}H_{25}O_3N$	3.74	3.86
24	H	4-(2-Phentylethyl)	277–278	90	$C_{23}H_{17}O_3N$	3.94	3.92
25	H	4-(3-Phenylpropyl)	175–179	80	$C_{24}H_{19}O_3N$	3.80	3.94
26	H	4-(4-Phenylbutyl)	224–227	85	$C_{25}H_{21}O_3N$	3.62	3.74
27	H	4-(2-Chlorophenylethyl)	213–214	75	$C_{23}H_{16}O_3N$	3.60	3.69
28	H	4-Carbomethoxy	310–313	49	$C_{17}H_{11}O_5N$	4.53	4.46
29	H	3-Carboxamide	>340	48	$C_{16}H_{10}O_4N_2$	9.52	9.43
30	H	4-Carboxy	>340	73	$C_{16}H_9O_5N$	4.73	4.69
31	H	3-Carboxy	>340	55	$C_{16}H_9O_5N$	4.73	5.02
32	H	4-Acetylamino	>356	65	$C_{17}H_{12}O_4N_2$	9.10	8.94
33	H	4-*N*-Phenylcarbamyl	>340	93	$C_{22}H_{14}O_2N_2$	7.56	7.41
34	H	4-*N*-(4-Methylphenyl)-carbamyl	>340	42	$C_{23}H_{16}O_4N_2$	7.23	7.22
35	H	4-*N*-(2,5-Dichlorophenyl)-carbamyl	121–125	32	$C_{22}H_{12}O_4N_2Cl_2$	6.38	6.34
36	H	3-*N*-(2,5-Dichlorophenyl)-carbamyl	138–139	79	$C_{22}H_{12}O_4N_2Cl_2$	6.38	6.29
37	NO_2	H	280 dec.	65	$C_{15}H_8O_5N_2$	9.44	9.31
38	NO_2	4-Methyl	320 dec.	60	$C_{16}H_{10}O_5N_2$	9.02	8.82
39	NO_2	4-(1-Pentyl)	220–224	62	$C_{20}H_{18}O_5N_2$	7.67	7.78
40	NO_2	4-(1-Hexyl)	192–194	73	$C_{21}H_{20}O_5N_2$	7.36	7.70
41	NO_2	4-(1-Octyl)	179–182	60	$C_{23}H_{24}O_5N_2$	6.86	6.78
42	NO_2	4-(1-Nonyl)	173–176	60	$C_{24}H_{26}O_5N_2$	6.63	6.55
43	NO_2	4-Cyclohexylmethyl	227–230	70	$C_{22}H_{20}O_5N_2$	7.14	6.95
44	NO_2	4-(4-Ethylcyclohexylmethyl)	180–183	35	$C_{24}H_{24}O_5N_2$	6.66	6.60
45	NO_2	4-Ethyl-3-methyl	295–297	35	$C_{18}H_{14}O_5N_2$	8.28	8.05

acetic acid solution, a good yield of orange product (II) was obtained. Although acetic acid mixed with other solvents could be used in the reaction, acetic acid (1–2% water) was superior to the various other mixtures.

The betaine structure II is evidenced by its high

melting point and considerable water solubility. However, the melting point is lowered when an alkyl radical is attached to the pyridinium ring and the water solubility also decreases. On the other hand, when a carboxyl group is on the pyridinium ring, the melting point is higher. This is probably due to the fact that the betaine formation involved the carboxylate ion.

The colored compounds of structure II are insoluble in sodium hydroxide but dissolve in concentrated hydrochloric acid to give faintly yellow solutions; the original compound is regenerated by dilution with water. A white compound can be precipitated from the concentrated acid solution, and it is extremely hygroscopic and contains ionic halogen in excess of one ion per molecule. Water converts this material to the original orange compound.

When a 2-alkylpyridine was used in the reaction a dark gummy mass was obtained, and only when the reaction mass was heated for several hours was it possible to secure a deep red, crystalline product. 3- or 4-Alkylpyridines gave bright yellow to orange colored compounds. The 2-alkylpyridinium compounds were less soluble in concentrated hydrochloric acid than were the 3- and 4-alkylpyridinium products. 2-Chloropyridine did not react even after prolonged heating with 2,3-dichloro-1,4-naphthoquinone. 2,3-Dichloro-5-nitro-1,4-naphthoquinone[5] reacted very readily with pyridine and substituted pyridines although the yields of betaines (II) were generally lower than when 2,3-dichloro-1,4-naphthoquinone was used.

The catalytic reduction of 1-(1,4-dihydro-1,4-dioxo - 3 - hydroxy - 2 - naphthyl)pyridinium betaine has been studied. This compound readily absorbs four moles of hydrogen in the presence of platinum catalyst which indicates the reduction of the quinone to hydroquinone and the pyridinium ring to the piperidine ring. The ease of this reduction is further indication of the pyridinium structure (II) since it is well known that pyridinium compounds are readily reduced to piperidine compounds under these conditions.[6] However, the orange quinone (III), and not the colorless hydroquinone, was isolated from the reduction since the hydroquinone was readily oxidized by air during the filtration process.

The 1-(1,4-dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)pyridinium inner salts described in the present communication were tested by Dr. Paul E. Thompson and co-workers[7] at Parke, Davis and Company against *Endamoeba histolytica in vitro*[8] and when indicated against experimentally induced *E. histolytica* infections in rats.[9] Although details of these test results will be reported elsewhere, it is of interest to note that while the parent 1-(1,-4-dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)pyridinium inner salt was essentially devoid of antiamebic activity, related compounds with alkyl groups containing from six to twelve carbon atoms *para* to the pyridine nitrogen (compounds 6, 7, 15, 18, 20, and 23) were amebicidal *in vitro* at concentrations of 2 to 37 μg./ml., and all of them were active against intestinal amebiasis in rats.

EXPERIMENTAL

1-(1,4-Dihydro-1,4-dioxo-3-hydroxy-2-naphthyl)-4-(1-octyl)-pyridinium betaine (II). Twenty grams of 4-(1-octyl)pyridine in 20 ml. of acetic acid was added rapidly to a solution of 23 g. of 2,3-dichloro-1,4-naphthoquinone in 250 ml. of acetic acid at 100°. The temperature of the solution was maintained at 100–110° for 1 hr. The mixture was cooled and diluted with 250 ml. of ice water. The crystals were removed and recrystallized from acetic acid–water solution, then from dimethyl formamide. The yield was 70%, m.p. 230–231° (corrected).

Other compounds of this type were prepared in the essentially same manner except that with the 2-alkylpyridines the reaction time was extended to 5 or 6 hr. The data are summarized in Table I.

The pyridines used in the work were obtained from Reilly Tar and Chemical Corporation and were distilled or recrystallized before use.

2-Hydroxy-3-piperidine-1,4-naphthoquinone. A suspension of 10 g. of 1-(1,4-dihydro-3-hydroxy-1,4-dioxo-2-naphthyl)-pyridinium betaine and 0.2 g. of platinium oxide in 100 ml. of ethanol was reduced by shaking at room temperature with hydrogen at the pressure of 45 p.s.i. Four moles of hydrogen were absorbed in about 15 min. The solution was colorless but turned red when exposed to air. The solution was evaporated and cooled and 4.7 g. (50%) of orange crystals, which melted at 192–193°, was obtained. This compound formed a red-purple solution with dilute sodium hydroxide and was insoluble in dilute hydrochloric acid.

Anal. Calcd. for $C_5H_{15}NO_3$: C, 70.02; H, 5.87; N, 5.44. Found: C, 69.88; H, 5.92; N, 5.51.

2-Hydroxy-3-(4-n-octylpiperidino)-1,4-naphthoquinone. This compound was prepared by the previous precedure in 60% yield. The orange crystals melted at 152–153°.

Anal. Calcd. for $C_{23}H_{31}NO_3$: C, 74.79; H, 8.41; N, 3.74. Found: C, 74.71; H, 8.63; N, 3.75.

2-Hydroxy-3-(4-n-hexylpiperidino)-1,4-naphthoquinone. A 60% yield of orange crystals of this compound, m.p. 155–157°, were obtained in a like manner.

Anal. Calcd. for $C_{21}H_{26}NO_3$: N, 4.12. Found: N, 4.15.

DENTON, TEX.

(5) O. Y. Imray, British Pat. No. 288,927, April 19, 1928.

(6) F. Krohnke (with S. Fosold), *Ber.*, **67**, 656 (1934).

(7) The authors are indebted to Dr. Paul E. Thompson, Miss Anita Bayles, and Mr. D. A. McCarthy for the antiamelic testing.

(8) For a description of test methods, see P. E. Thompson, J. W. Reinertson, D. A. McCarthy, A. Bayles, and A. R. Cook, *Antibiotics and Chemotherapy*, **5**, 433 (1955).

(9) For a description of test methods, see P. E. Thompson, M. C. Dunn, A. Bayles, and J. W. Reinertson, *Am. J. Trop. Med.*, **30**, 203 (1950).